A computer readable medium having recorded thereon SEQ ID NO:1 through SEQ ID NO:8283 is, by any definition, a composition of matter.

***Specification***

The disclosure was objected to because it contained an embedded hyperlink and/or other form of browser executable code. It is believed that the embedded hyperlink and/or other form of browser executable code have been removed from the specification in view of the indicated amendments to the specification, captioned above. Therefore it is respectfully requested that the Examiner remove this grounds of objection.

***Claim Rejections – 35 USC §112***

***§112-First***

The Examiner has rejected Claims 36-37 under §112 first paragraph as lacking sufficient enablement so that one skilled in the art would know how to use the claimed sequence, further specifying that there is no negative control set forth for probes and determining that it would be unclear if the sequences are detected by hybridization or by some other means, and a host of other limitations that the Examiner has read into the claims that are not present therein, finally finding that it is indiscernible how someone of skill in the art would use such an unknown entity. Furthermore, the Examiner determined that it would require an undue amount of experimentation to determine how to use a disclosed nucleic acid or to determine the activity or some other property of a disclosed nucleic acid, and asserts that the specification fails to teach the skilled artisan how to make and use the claimed invention. The Applicant respectfully traverses the Examiner's rejection.

It is unclear to the Applicant whether the Examiner has rejected the CLAIMS as lacking sufficient enablement, or whether the Examiner intended to reject claims because the SPECIFICATION lacks sufficient enablement. The Applicant was not aware that CLAIMS have ever been required, either by PTO practice as set forth in the MPEP or by statute or otherwise, to provide sufficient enablement. However, the Applicant believes that the Examiner INTENDED to refer to the SPECIFICATION. Therefore, the following argument addresses the sufficiency of enablement of the specification I view of the Examiner's remarks directed to the enablement issue.

The application sets forth what is believed to be a sufficient enablement of the scope of the claims 36 and 37. The scope of the claims encompasses (for Claim 36) a computer readable medium having recorded thereon one or more nucleotide sequences, wherein each of the nucleotide sequences is selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 8283 or complements thereof, and further (for Claim 37, dependent on Claim 36) the nucleotide sequences or complements thereof are limited to sequences that encode *B. thuringiensis* proteins or polypeptides. The specification, in the sequence listing, sets forth the 8283 nucleotide sequences that are to be recorded onto the computer readable medium. The specification, in Table 1, sets forth all of the protein or polypeptide sequences believed to be encoded by the nucleotide sequences as set forth in the 8283 nucleotides sequences set forth in the sequence listing. The specification sets forth how one would go about using the computer readable medium having the plurality of nucleotide sequences recorded thereon, for example from about line 26, page 51 through about line 6, page 59, the means available in the art for using such computer readable media, and the means, including algorithms for searching and comparisons, that one skilled in the art would employ in using the sequences of the present invention provided in a computer readable medium format. There would, contrary to the Examiner's assertion, be no need or requirement for a probe, no negative control, no physical hybridization, no inhibition, no treatment, and no requirement to know what use a particular sequence could be applied to. It is surprising that the Examiner and the PTO take this stance because the Examiner has utilized a similar but different computer readable medium to accomplish a comparison at least of SEQ ID NO:1 to determine whether SEQ ID NO:1 has been identified as being present, whether by complete complementarity, complete identity, or otherwise, to any of the other sequences available in the computer readable media available to the Examiner on which are recorded a plurality of nucleotide sequences. If the Examiner is capable of discerning how to use a computer readable medium to compare for identity, complementarity, or otherwise, only one of the sequences identified in the Applicant's specification, then one skilled in the art would most certainly be capable of discerning how to use the Applicant's computer readable medium onto which is recorded one or more nucleotide sequences of the present invention. It would not require undue experimentation to determine activity or property

of one or more of the disclosed nucleic acids because the skilled artisan is taught, in the pages specified above, what algorithms to use, where to find the algorithms, what databases to use and where to find those, and whether to make a comparison for identity, complementarity, or otherwise. The specification, in particular in Table 1, sets forth sufficient direction AND guidance as to what peptides each nucleotide sequence encodes, the level of homology, identity, and/or complementarity identified based on a search of all other nucleotide and protein sequences known and available at the time the application was filed, and therefore provides a plurality of working examples directed to the same. The claims are not believed to be overbroad because claims are not required to recite particular biological activities. Therefore, in view of the foregoing, it is believed that the claims as filed, and even as now amended, sufficiently enable the skilled artisan how to make and use the claimed invention, which is a composition that is useful in identifying a nucleic acid sequence obtained from a *Bacillus* species comprising a computer readable medium having recorded thereon one or more nucleotide sequences, wherein each of the nucleotide sequences is selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 8283 or complements thereof, and furthermore, wherein the nucleotide sequences or complements thereof are limited to sequences that encode *B. thuringiensis* proteins or polypeptides. It is respectfully requested that the Examiner remove this grounds of rejection.

***§112-Second***

The Examiner has rejected Claims 36-37 under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. In particular, the Examiner has identified that Claims 36 and 37 are indefinite due to the lack of clarity of the phrase "or complements thereof" and has required the Applicant to amend the claims so that the phrase, and in particular the word "complements" is limited to a specific degree of complementarity. The Applicant traverses this rejection.

The specification as filed, at page 9, lines 15-18, sets forth the definition of the word "complement" and "complementarity". It is believed that the specification

therefore adequately defines the phrase that the Examiner has indicated lacks clarity. The specification states that

> "a nucleotide sequence is ...the "complement" of another nucleotide sequence if they exhibit complete complementarity. As used herein, molecules are said to exhibit "complete complementarity" when every nucleotide of one of the sequences is complementary to a nucleotide of the other."

Therefore, based on the written description in the specification as filed, it is believed that the indicated phrase does not lack clarity and is therefore not indefinite, and the claims have not, with reference to the indicated limitation, been amended. It is respectfully requested that the Examiner remove this grounds of rejection.

*35 USC §103.*

The Examiner rejected Claim 36 under 35 USC §103(a) as being unpatentable in view of Bret et al. and provided no citation to the Bret et al. reference. In addition, the Examiner asserted that the Applicant's SEQ ID NO:1 was 54.3% similar in the best matching locality to a sequence disclosed in Bret et al., in particular since the Applicant's claims did not define the degree of complementarity required. It was unclear what reference/citation the Examiner was referring to, and so the Applicant's attorney and the Examiner discussed this matter by telephone conference on March 5, 2003. The Examiner indicated during the telephone conference that the reference to Bret et al. was in error, and that the Examiner was actually referring to a US Patent No. 6,037,123, naming a plurality of co-inventors and a Bret Benton as the first named co-inventor. Therefore, the Examiner indicated that the citation should have been to Benton et al. and not to Bret et al. Furthermore, the Examiner indicated that the Benton et al. reference contained a sequence, SEQ ID NO:12, that corresponded to the Applicant's SEQ ID NO:1, exhibiting the features as indicated above. The Applicant herewith traverses the Examiner's rejection.

Interview held OK CLS 5/15/03

In view of the argument set forth under §112, second paragraph, it is believed that the Examiner's §103 rejection is obviated. The Applicant has established that "complement", as defined by the specification, refers to complete complementarity, i.e., a

one for one base alignment along the length of the nucleotides being compared. Therefore, since Benton et al. SEQ ID NO:12 is no where near 100% identity to SEQ ID NO:1, it is believed that the §103 rejection is obviated, and it is respectfully requested that the Examiner remove this grounds of rejection.

It is respectfully requested that the Examiner find the claims in condition for allowance. If there are minor technicalities that need attending to, the Examiner is requested to contact the undersigned attorney at the indicated telephone number.

Respectfully submitted,

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**Clean Copy of the Amendments to the Specification**

[paragraph bridging pages 2-3]

*Bacillus thuringiensis* is a spore-forming Gram-positive bacterium. During sporulation, *B. thuringiensis* produces proteinaceous inclusions which are composed of proteins known as insecticidal crystal proteins (ICPs), Cry proteins, or delta-endotoxins. These proteins are toxic to a variety of insect species including orders Lepidoptera, Coleoptera, Diptera, Hemoptera, Hymenoptera, Orthoptera, and Mallophaga and to nematodes, mites, and protozoa (Beegle and Yamamoto, *Can. Entomol. 124*:587-616; Feitelson, Advanced Engineered Pesticides (L. Kim, *ed.*), Marcel Dekker, Inc., New York (1993), pp. 63-71; Feitelson, *et al., Bio/Technology 10*:271-275; U.S. Patent No. 4,948,734 (1990)). Due to their high specificity for particular insect pests and their safety for man and the environment, ICPs have been used as biopesticides for the last three decades. Using molecular genetic techniques, numerous delta-endotoxin genes have been isolated and their DNA sequences determined. The cloning and sequencing of a number of δ-endotoxin genes from a variety of *B. thuringiensis* strains has been described and are summarized by Schnepf *et al.* ( *Microbiol. Mol. Biol. Rev. 62*:775-806, *Bacillus thuringiensis* And Its Pesticidal Crystal Proteins, 1998). The nomenclature and appearance of newly identified genes is summarized and regularly updated at by Crickmore, N., Zeigler, D.R., Schnepf, E., Van Rie, J., Lereclus, D., Baum, J, Bravo, A. and Dean, D.H. "*Bacillus thuringiensis* toxin nomenclature" at the University of Sussex Department of Biology web site biols.susx.ac.uk/home/neil_crickmore/bt. These genes have been used to develop certain genetically engineered *B. thuringiensis* products that are in commercial use. Recent developments have seen new δ-endotoxin delivery systems developed, including genetically engineered plants that contain and express δ-endotoxin genes. *Bacillus thuringiensis* is a key source of genes, which when modified can be used for transgenic expression to provide pest resistance in plants.

[last full paragraph, page 21]

Open reading frames in genomic sequences can be screened for the presence of protein homologues utilizing a number of different search algorithms that have been developed, one example of which is the suite of programs referred to as BLAST programs. There are five implementations of BLAST, three designed for nucleotide sequences queries (BLASTN, BLASTX, and TBLASTX) and two designed for protein sequence queries (BLASTP and

TBLASTN) (Coulson, *Trends in Biotechnology 12:*76-80 (1994); Birren *et al., Genome Analysis 1:*543-559 (1997)). Other examples of suitable programs that can be utilized are well known in the art. In addition, unidentified reading frames may be screened for by gene prediction software such as GenScan, which is located at the Stanford University web site gnomic.Stanford.edu/GENSCANW.html. Novel genes, i.e., with no known homologs, can be predicted with the program GeneMark, which calculates the probability of a gene based on the presence of a gene-like 'grammar' in the DNA sequence (i.e., start and stop signals, and a significant open reading frame) and statistical analyses of protein-coding potential through biases in putative codon usage (see the Georgia Tech University web site genemark.biology.gatech.edu/GeneMark for details).

[paragraph bridging pages 13-14]

Another example of algorithm that is suitable for determining sequence similarity is the BLAST algorithm, which is described in Altschul et al, J. Mol. Biol. 215: 403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (NCBI) web site ncbi.nlm.nih.gov; see also Zhang, Genome Res. 7:649-656 (1997) for the "PowerBLAST" variation. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al, J. Mol. Biol. 215: 403-410 (1990)). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a wordlength (W) of 11, the BLOSUM62 scoring matrix (see Henikoff, Proc. Natl. Acad. Sci. USA 89:10915-10919(1992)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands. The term BLAST refers to the BLAST algorithm which performs a statistical analysis of the similarity between two sequences; see, e.g., Karlin, Proc. Natl. Acad. Sci. USA 90:5873-5787 (1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two

nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

[paragraph bridging pages 35 and 36]

Exogenous genetic material may be transferred into a plant cell by the use of a DNA vector or construct designed for such a purpose. Vectors have been engineered for transformation of large DNA inserts into plant genomes. Binary bacterial artificial chromosomes have been designed to replicate in both *E. coli* and *A. tumefaciens* and have all of the features required for transferring large inserts of DNA into plant chromosomes as set forth in the protocol by Choi and Wing, available at the Clemson University web site genome.Clemson.edu/protocols2-nj.html, July, 1998. ApBACwich system has been developed to achieve site-directed integration of DNA into the genome. A 150 kb cotton BAC DNA is reported to have been transferred into a specific *lox* site in tobacco by biolistic bombardment and *Cre-lox* site specific recombination.

[page 55, second full paragraph]

It is well known to a person skilled in the art that the sequence data from a large scale shotgun sequencing project can be processed and assembled into contigs, which represent a reconstruction of the original chromosomal genome sequence from the cloned fragments. Programs are available in the public domain that can analyze the sequence output and assemble the sequences into larger sequence regions representing contiguous sequences of the target genome. Examples of such programs can be found at, for example, the following web sites: genome.wustl.edu/gsc, sanger.ac.uk, and mbt.washington.edu. An example of a sequence reading program is Phred which can be found at the University of Washington web site mbt.washington.edu. Phred reads DNA sequencer trace data, calls bases, assigns quality values to the bases, and writes the base calls and quality values to output files.

[page 55, third full paragraph]

The process of assembling DNA sequence fragments generally involves three phases; the overlap phase, the layout phase and the multi-alignment, or consensus, phase. In the overlap phase, each fragment is compared against every other fragment to determine if they share a common subsequence, an indication that they were potentially sampled from overlapping stretches of the original DNA strand. Pairs of fragments are compared in two ways; 1) with both

fragments in the same relative orientation, and 2) with one of the fragments having been reverse complemented. In the layout phase, a series of alternate assemblies or layouts of the fragments based on the pairwise overlaps is generated. A layout specifies the relative locations and orientations of the fragments with respect to each other and is typically visualized as an arrangement of overlapping directed lines, one for each fragment. The general criterion for the layout phase is to produce plausible assemblies of maximum likelihood. In this manner, it can be determined if there is more than one way to put the pieces together and if different solutions appear equally plausible. In such a case, one would return to the lab and obtain additional information to resolve the ambiguity. The multi-alignment, or consensus, phase uses more information than just the pairwise alignments in the layout. The sequences of all the fragments in a layout are simultaneously aligned, giving a final set of contigs representing regions of the target genome. An example of an assembly program is PHRAP, which can be found at the University of Washington web site chimera.biotech.washington.edu/UWG/tools/phrap.htm.

[page 56, second full paragraph]

Similarity analysis includes database search and alignment. Examples of public databases include the DNA Database of Japan (DDBJ) website ddbj.nig.ac.jp; Genebank website ncbi.nlm.nih.gov/web/genbank/index.html; and the European Molecular Biology Laboratory Nucleic Acid Sequence Database (EMBL) website ebi.ac.uk/ebi_docs/embl_db.html. A number of different search algorithms have been developed, one example of which are the suite of programs referred to as BLAST programs. There are five implementations of BLAST, three designed for nucleotide sequences queries (BLASTN, BLASTX, and TBLASTX) and two designed for protein sequence queries (BLASTP and TBLASTN) (Coulson, *Trends in Biotechnology 12:*76-80 (1994); Birren *et al., Genome Analysis 1:*543-559 (1997)).

[page 63, first full paragraph]

After the base calling is completed, sequence preprocessing is performed. Quality assessment and trimming is performed by determining the maximum scoring segment of PHRED quality score > 10. Cloning sequences are removed by utilizing cross_match, available at the University of Washington website mbt.washington.edu, and searching a database of relevant cloning sequences. Contaminating sequences (E. coli, yeast, vector, linker) are then removed from the dataset by utilizing cross_match to search a database of contamination sequences.

[page 63, second full paragraph]

The preprocessed sequences are then assembled into contigs, or groups of overlapping sequences. Contigs are assembled using PHRAP (phragment assembly program), also developed by Green and available at the University of Washington web site mbt.washington.edu, using default assembly parameters. This program takes a file of shotgun sequences and compiles consensus contig sequences. Alignments are influenced by quality scores, based on Green's algorithm. Singletons are the remaining sequences without sufficient overlaps with others after the assembly.

**Clean Copy of the Claims**

36. (Amended) A composition for use in identifying a nucleic acid sequence obtained from a *Bacillus* species comprising a computer readable medium having recorded thereon one or more nucleotide sequences, wherein each of the nucleotide sequences is selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 8283 or complements thereof.

37. (Amended) The composition according to claim 36, wherein each of the nucleotide sequences or complements thereof encodes a *B. thuringiensis* protein or polypeptide.

51. (New) A composition for use in identifying a nucleic acid sequence obtainable from a *Bacillus thuringiensis* species comprising a computer readable medium having recorded thereon one or more nucleotide sequences selected from the group consisting of SEQ ID NO:1 through SEQ ID NO:8283, wherein said nucleic acid sequence encodes a protein selected from the group consisting of an insect inhibitory protein and an antibiotic biosynthesis protein.

52. (New) A composition for use in a method for identifying a nucleic acid sequence obtained from a *Bacillus thuringiensis* species comprising a first computer readable medium having recorded thereon one or more nucleotide sequences selected from the group consisting of SEQ ID NO:1 through SEQ ID NO:8283, said method comprising the steps of:

a) isolating and purifying total DNA from a *Bacillus thuringiensis* species;
b) constructing a library of DNA clones from the isolated and purified total DNA;
c) identifying the nucleotide sequences of each clone and making the nucleotide sequences available on a second computer readable medium;
d) comparing the nucleotide sequences available in said second computer readable medium with the sequences on said first computer readable medium, and
e) subtracting sequences from said second computer readable medium that exhibit complete complementarity with sequences from said first computer readable medium;

wherein one or more sequences remaining in said second computer readable medium encode proteins selected from the group consisting an insect inhibitory protein and an antibiotic biosynthesis protein.

53. (New) A composition for use in identifying a nucleic acid sequence obtained from a *Bacillus* species comprising a computer readable medium having recorded thereon one or more nucleotide sequences, wherein each of the nucleotide sequences is selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 8283 or complements thereof, and wherein sequence identity between said nucleic acid sequence obtained from said *Bacillus* species and said nucleotide sequences or complements thereof recorded on said computer readable medium are optimally aligned for comparison using a nucleotide sequence alignment means.